IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Division Under 37 C.F.R. 1.53(b)
Application of: Lee et al.

Prior Application Serial No.: 08/951,873
Prior Filing Date: October 17, 1997

Prior Group Art Unit: 1614

Anticipated Classification of this Application:
Class 514 Subclass 243.000

Examiner: J. Goldberg

For: 1,2,4-BENZOTRIAZINE OXIDES AS RADIOSENSITIZERS AND SELECTIVE CYTOTOXIC AGENTS

CERTIFICATE UNDER 37 C.F.R. 1.10

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Geraldine D Shea

Signature

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the specification:

On page 1, immediately after the title of the invention insert the following cross reference to related application section:

--Cross Reference to Related Applications

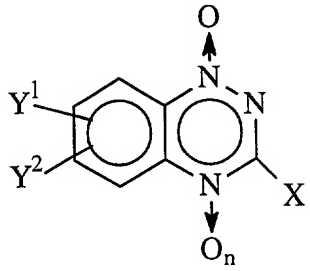
This application is a divisional of prior copending application, Serial No. 08/951,873, filed October 17, 1997, which is a division of application Serial No. 08/453,329 filed May 30, 1995, Patent No. 5,849,738, which is a division of application Serial No. 08/378,420 filed January 26, 1995, Patent No. 5,616,584, which is a division of application Serial No. 07/939,787 filed October 27, 1992, abandoned, which is a division of application Serial No. 07/409,480 filed September 18, 1989, Patent No. 5,175,287, which is a continuation-in-part of application Serial No. 07/356,602 filed May 24, 1989, abandoned, which is a continuation of application Serial No. 07/169,873 filed March 18, 1988, abandoned, which is a continuation-in-part of application Serial No. 911,906 filed September 25, 1986, abandoned.--

In the claims:

Please cancel claims 2, 5-7, 9, 12-27, and 46-53, amend claims 1, 3, 4, 8, and 10, and add new claims 54 and 55 as follows before calculating the filing fee for the above-identified application.

Please amend claims 1, 3, 4, 8, and 10 to read as follows:

1. (Amended) A method of selectively killing hypoxic tumor cells sensitive to the compounds of the formula in a host comprising administering to said host an effective amount of a pharmaceutical composition comprising a compound of the formula



wherein X is H; hydrocarbyl (1-4C) substituted with OH, NH_2, NHR or NRR; halogen; OH; or C_1-C_4-alkoxy where each R is independently an alkyl of 1-4 carbon atoms or acyl of 1-4 carbon atoms, or wherein in the case of NRR the two R groups may be linked together to form a morpholino, pyrrolidino or piperidino ring, and wherein R may be further substituted with OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substituents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; alkoxy (1-6C); hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycabonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-0-) linkage; or wherein Y^1 and Y^2 are independently either

morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents, or a pharmacologically acceptable salt of said compound.

3. (Amended) The method of claim 1 wherein Y^1 and Y^2 are both H.

4. (Amended) The method of claim 1 wherein Y^1 is H and Y^2 is nitro.

8. (Amended) The method of claim 54 wherein X is H.

10. (Amended) The method of claim 54 wherein Y^1 and Y^2 are both H.

Please cancel claims 2, 5-7, 9, 12-27, and 46-53 and add the following new claims:

54. (New) A method according to Claim 1 wherein X is H or hydrocarbyl (1-4C) substituted with OH, NH_2, alkoxy (1-4C) or halogen.

55. (New) A method according to Claim 54 wherein X is hydrocarbyl (1-4C) substituted with an alkoxy(1-4C) group.

REMARKS

The specification has been amended in order to update the cross-reference to related application information.

Claims 2, 5, 6, 9, 12-27, and 46-53, which are directed to subject matter which was elected for prosecution in prior application are canceled. Claim 7 is canceled and replaced by new claim 54.

Claim 1 is amended to exclude therefrom the subject matter elected for prosecution in the parent application and to correspond to the format of the claims allowed in the parent. Support for the amended definition of X is found in the specification at page 5, line 9, to page 6, line 18, and the amendment of the definition of Y^1 and Y^2 to include alkoxy (1-6C) finds support in the specification, for example, at page 14, line 33; page 15, lines 1, 4, and 5; page 19, lines 4, 5, 8, 9, 12-14, 25, and 26, and page 21, lines 30 and 31.

New claim 55 further limits claim 54 to the compounds in which X is C_1-C_4-alkoxy-substituted C_1-C_4-alkyl.

Claims 1, 3, 4, 8, 10, 11, 28-45, 54, and 55 are in the application as amended.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Dated: 12/17/01

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Version With Markings to Show Changes Made

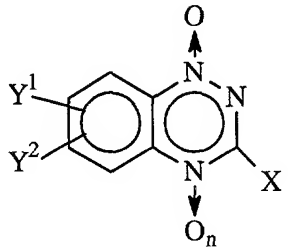
In the specification

On page 1, immediately after the title of the invention, a cross reference to related application section was inserted.

In the Claims:

Claims 1, 3, 4, 8, and 10 have been amended as follows:

1. (Amended) A method of selectively killing hypoxic tumor cells sensitive to the compounds of the formula in a host comprising administering to said [cells] host an effective amount of a pharmaceutical composition comprising a compound of the formula



wherein X is H; hydrocarbyl (1-4C) substituted with OH, NH_2, NHR or NRR; halogen; OH; or C_1-C_4-alkoxy where each R is independently an alkyl of 1-4 carbon atoms or acyl of 1-4 carbon atoms, or wherein in the case of NRR the two R groups may be linked together to form a morpholino, pyrrolidino or piperidino ring, and wherein R may be further substituted with OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substituents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; alkoxy (1-6C); hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof,

acetylaminoalkyl (1-4C), carboxy, alkoxycabonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-0-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents, or a pharmacologically acceptable salt of said compound.

3. (Amended) The method of claim [2,] 1 wherein Y^1 and Y^2 are both H.

4. (Amended) The method of claim [2,] 1 wherein Y^1 is H and Y^2 is nitro.

8. (Amended) The method of claim [7,] 54 wherein X is H.

10. (Amended) The method of claim [7,] 54 wherein Y^1 and Y^2 are both H.

Claims 2, 5-7, 9, 12-27, and 46-53 have been canceled and new claims 54 and 55 have been added.